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Chronic obstructive pulmonary disease and cardiac repolarization: data from a randomized controlled trial

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Abstract: Background: Altered cardiac repolarization is a risk factor for sudden cardiac death and seems to be increased in chronic obstructive pulmonary disease (COPD) patients. Objective: Lung volume reduction surgery (LVRS) has been shown to improve breathing mechanics and lung function in patients with severe COPD and emphysema and possibly also improve altered cardiac repolarization. Methods: Thirty patients scheduled for LVRS were randomized to LVRS or to the control group. We investigated the treatment effect 3 months after LVRS on measures of cardiac repolarization and dispersion of repolarization (QTc interval, QT dispersion) derived from electrocardiography. Univariable and multivariable analyses were used to identify possible confounders influencing the treatment effect. Results: LVRS was associated with an improvement in lung function (mean \pm SD residual volume/total lung capacity of $-9 \pm 11\%$ and forced expiratory volume in 1 s of $+30 \pm 29\%$). LVRS did not significantly reduce QTc (median -5.3 ms, 95% confidence interval, CI -15.5 to 3.7 , $p = 0.214$) and QT dispersion (median -3.0 ms, 95% CI -13.0 to 7.0 , $p = 0.536$) compared to the control group. No significant association between change in QTc and change in QT dispersion, respectively, and change in possible confounders was found. Conclusion: LVRS seems to have no effect on cardiac repolarization in patients with COPD. Thus, lung hyperinflation seems not to be a causal mechanism for altered cardiac repolarization in COPD patients.

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Chronic Obstructive Pulmonary Disease and Cardiac Repolarization: Data from a Randomized Controlled Trial

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Key Words

Airflow limitation · Cardiac repolarization · Chronic obstructive pulmonary disease · Sudden cardiac death · Surgery for emphysema

Abstract

Background: Altered cardiac repolarization is a risk factor for sudden cardiac death and seems to be increased in chronic obstructive pulmonary disease (COPD) patients. **Objective:** Lung volume reduction surgery (LVRS) has been shown to improve breathing mechanics and lung function in patients with severe COPD and emphysema and possibly also improve altered cardiac repolarization. **Methods:** Thirty patients scheduled for LVRS were randomized to LVRS or to the control group. We investigated the treatment effect 3 months after LVRS on measures of cardiac repolarization and dispersion of repolarization (QTc interval, QT dispersion) derived from electrocardiography. Univariable and multivariable analyses were used to identify possible confounders influencing the treatment effect. **Results:** LVRS was associated with an improvement in lung function (mean \pm SD residual volume/total lung capacity of $-9 \pm 11\%$ and forced expiratory volume in 1 s of $+30 \pm 29\%$). LVRS did not significantly reduce QTc (median -5.3 ms, 95% confidence interval, CI

-15.5 to 3.7 , $p = 0.214$) and QT dispersion (median -3.0 ms, 95% CI -13.0 to 7.0 , $p = 0.536$) compared to the control group. No significant association between change in QTc and change in QT dispersion, respectively, and change in possible confounders was found. **Conclusion:** LVRS seems to have no effect on cardiac repolarization in patients with COPD. Thus, lung hyperinflation seems not to be a causal mechanism for altered cardiac repolarization in COPD patients.

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Introduction

Cardiovascular disease plays an important role regarding the morbidity and mortality in patients with chronic obstructive pulmonary disease (COPD) [1–3]. It has been suggested that the rate of sudden cardiac death (SCD) is two- to threefold increased in patients with COPD [4]. A recently published cross-sectional study by our group found that a high prevalence of COPD patients showed altered cardiac repolarization and increased dispersion of repolarization, potentially exposing these patients to an increased risk of malignant ventricular arrhythmias and SCD [5].

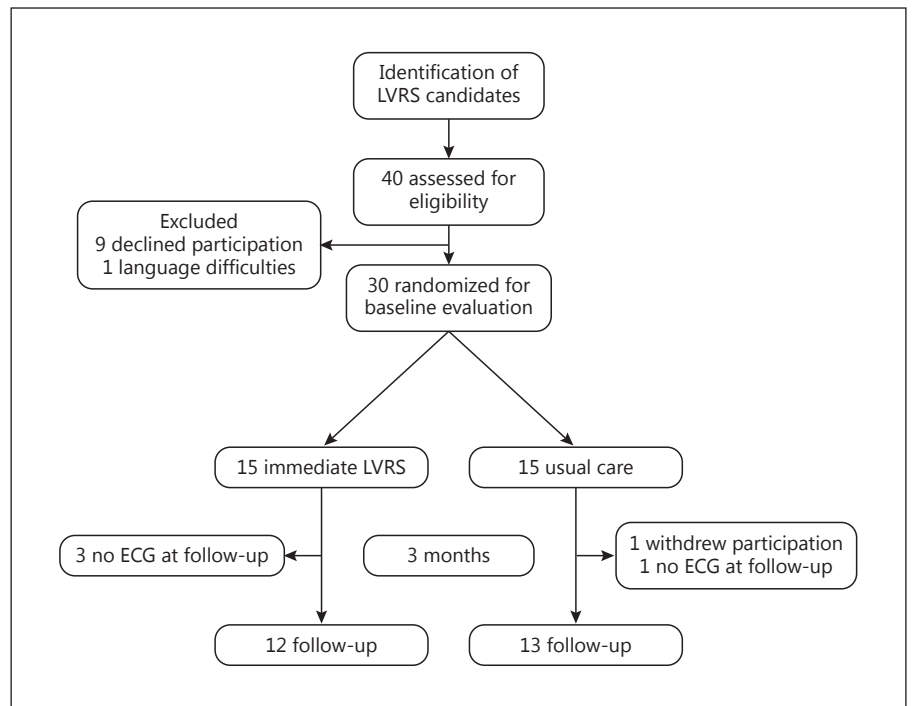


Fig. 1. Study flowchart.

Prolonged cardiac repolarization is associated with the development of fatal arrhythmias and the occurrence of SCD [6–8]. Different measures derived from electrocardiography (ECG) represent repolarization inhomogeneities of the myocardium such as QT interval and QT dispersion [8, 9]. In diverse patient populations, an association between altered cardiac repolarization and the development of malignant arrhythmia and SCD, respectively, has been documented [10–12].

The degree of airflow limitation measured by forced expiratory volume in 1 s (FEV₁) is associated with a higher risk of ischemic heart disease and SCD, even after adjusting for the cardiovascular risk profile [13, 14]. Further, COPD patients seem to have a higher frequency of arrhythmias, and the severity of airflow obstruction seems to be associated with the occurrence of arrhythmia in COPD patients [15, 16].

A small case-control study with 30 COPD patients and 31 age- and sex-matched control subjects showed an association between increased maximal QT interval and the development of ventricular arrhythmia [17]. However, the mechanisms contributing to altered cardiac repolarization in patients with COPD are still a matter of debate.

Apart from lung transplantation, lung volume reduction surgery (LVRS) is currently the only treatment that significantly improves airflow obstruction, but this ther-

apy is reserved for a highly selected group of patients with end-stage COPD. The aim of this study was to evaluate the treatment effect of LVRS on cardiac repolarization and to investigate possible influencing factors in a group of severe COPD patients.

Methods

Study Design and Subjects

The current analysis was a sub-study of a randomized controlled trial (RCT) evaluating the effect of LVRS on endothelial function in patients with severe COPD [18]. Randomization was performed 1:1 to intervention or control group. Patients with COPD (GOLD stages 3–4) planned for LVRS were randomized to one of two groups: group 1 receiving immediate LVRS (surgical approach described in the online suppl. material; for all online suppl. material, see www.karger.com/doi/10.1159/000445030) and group 2 receiving LVRS after a delay of 3 months. The same outcomes were measured at baseline and 3 months after LVRS and no therapy (control group), respectively (fig. 1). Sealed envelopes were used for the allocation procedure by M.K. No minimization was performed.

Patients between 40 and 75 years referred for evaluation of LVRS were included in the study at the University Hospital of Zurich, Switzerland, between November 2009 and April 2014. Election for LVRS was based on previously published criteria from the National Emphysema Treatment Trial [19] and interdisciplinary discussion with the department of thoracic surgery. Homogeneous

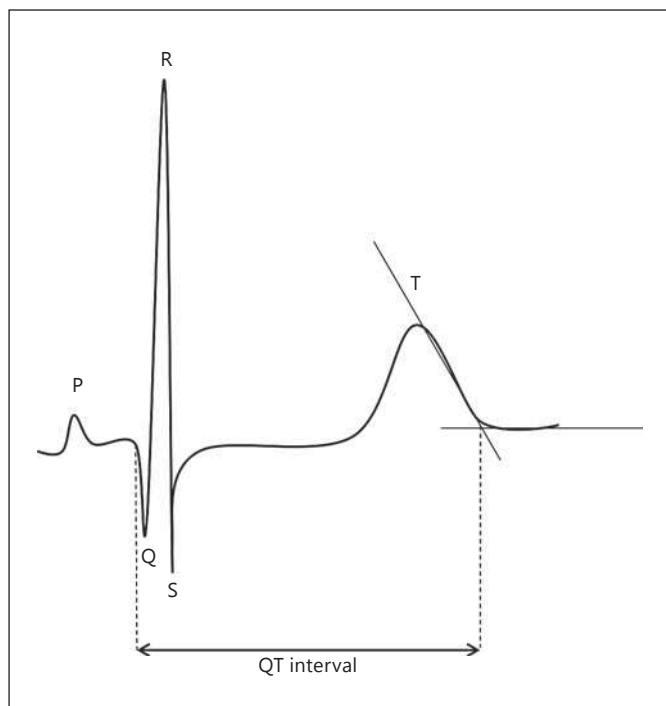


Fig. 2. The length of the QT interval was obtained by identifying the QRS onset and the point at which the downward slope of the T wave returns to baseline.

emphysema types were not generally excluded. Patients with an exacerbation within the last 6 weeks and mentally or physically disabled persons precluding informed consent or compliance with the protocol were also excluded.

The study was conducted in accordance with the declaration of Helsinki of the World Medical Association. The Ethics Committee of the Canton of Zurich approved the study (EK-ZH-NR: 1734) and all subjects gave written informed consent to participate. The study was registered at clinicaltrials.gov (NCT01020344).

Measurements

Cardiovascular Risk and Medication

The cardiovascular risk profile was assessed by the Pocock risk score, which predicts the individuals' 5-year risk of death due to a cardiovascular cause [20]. This score includes 11 cardiovascular risk factors, including sex, age, smoking status, systolic blood pressure, cholesterol, creatinine, height, diabetes, previous myocardial infarction, stroke and left ventricular hypertrophy. Brain natriuretic peptide (BNP) was measured from fresh plasma samples. Patients were asked if they used QT interval affecting medications according to the International Registry of Drug-Induced Arrhythmias maintained by the Georgetown University [21].

Blood Pressure and Heart Rate

Blood pressure and heart rate were measured after resting in supine position for 5 min with a validated blood pressure monitor (Omron Healthcare, Kyoto, Japan) in a quiet room. The average of three readings separated by 1-min intervals was used for analysis.

Respiratory Variables

Standard pulmonary functional testing was performed according to American Thoracic Society guidelines [22] to measure FEV₁, forced vital capacity (FVC), total lung capacity (TLC), residual volume (RV) and diffusing capacity of the lung for carbon monoxide (DLCO). Daytime arterial oxygen saturation (SaO₂) was measured by arterial blood gas analysis (ABL 700 series, Radiometer Copenhagen) after 5 min of rest.

Electrocardiography

Patients were asked to abstain from alcohol, tobacco or caffeine on the day the measurements were taken. All participants had to rest in supine position for at least 5 min before measurements were started. ECG was recorded with a 12-lead ECG (AT 104 PC, Schiller-Reomed AG, Switzerland) set at 25-mm/s paper speed and 10-mm/mV amplitude. Measurements of the ECG intervals were performed twice with dedicated ECG analysis software (DatInf® Measure 2.1d, DatInf GmbH, Tübingen, Germany) by two investigators who were blinded to the patient's data as previously described [23]. The mean of the ECG interval measurements by the two investigators was calculated and used for statistical analysis. Four consecutive heart cycles were evaluated for each lead. The mean value for each lead of the twelve leads was calculated. Figure 2 illustrates the calculation of repolarization measures. The QT interval was defined as the time from the earliest onset of the QRS complex to the end of the T wave [24]. The end of the T wave was defined as the cutting point of the tangent to the downward slope of the T wave and the isoelectric line [25]. As a measurement of dispersion of repolarization, QT dispersion was defined as the difference between the lead with the maximal and the lead with the minimal QT interval duration [26]. QT interval corrected for heart rate (QTc) was corrected for heart rate by using the Bazett formula [27].

Data Analysis and Statistics

Data analysis was performed on a per-protocol basis. All results are shown as mean values \pm standard deviation (SD) or median (quartiles) unless otherwise stated. Statistical analysis was performed with STATA 14 (StataCorp, College Station, Tex., USA). The treatment effect on cardiac repolarization was analyzed using multivariable regression models adjusting for treatment group and the corresponding baseline value. Further, univariable regression models were used to analyze the influence of treatment effect in possible confounders on cardiac repolarization. A post hoc analysis was performed to adjust change in cardiac repolarization for possible imbalances in baseline characteristics. A two-sided p value of <0.05 was considered to be statistically significant.

Results

Study Participants

Of the 40 patients screened for eligibility, 30 were included for baseline examination (fig. 1). Five patients were lost to follow-up. Of these, 1 patient withdrew participation and 4 patients (1 in the control group and 3 in the intervention group) had no ECG at follow-up. The baseline patient characteristics are shown in table 1.

Table 1. Baseline characteristics

	Control group (n = 13)	Intervention group (n = 12)
<i>Demographics and cardiovascular risk</i>		
Age, years	65 ± 6.1	64 ± 8.8
Male	9 (69)	7 (58)
Body mass index	23.9 ± 2.8	23.3 ± 5.2
Pack-years of smoking	53 ± 12.7	38 ± 7.8
Systolic blood pressure, mm Hg	130 ± 11.9	130 ± 9.3
Diastolic blood pressure, mm Hg	79 ± 10.2	86 ± 9.7
Heart rate, bpm	90.4 ± 15.0	78.1 ± 14.8
Arterial hypertension	16 (64)	9 (36)
Arrhythmia	2 (15)	1 (8)
Diabetes	3 (23)	3 (25)
Coronary artery disease	5 (38)	2 (17)
Pocock risk score, %	2.4 ± 1.4	2.1 ± 1.6
<i>Respiratory variables</i>		
FEV ₁ , % pred.	26 ± 5.9	27 ± 5.2
FVC, % pred.	68 ± 15.7	68 ± 10.8
TLC, % pred.	129 (119.0–130.0)	126 (118.5–150.5)
RV/TLC, %	67 ± 5.6	68 ± 4.6
DLCO, % pred.	35 ± 5.1	34 ± 8.3
SaO ₂ , %	94 (91.6–95.9)	95 (94.1–95.5)
<i>Medication</i>		
QT-affecting drug	3 (23)	3 (27)
Antihypertensive drug	9 (69)	5 (42)
Beta-blocker	2 (15)	0 (0)
Cholesterol-lowering drug	4 (31)	3 (25)
LAMA only	0 (0)	0 (0)
LAMA + GC	0 (0)	1 (8)
LABA only	1 (8)	0 (0)
LABA + GC	0 (0)	0 (0)
LAMA + LABA	0 (0)	1 (8)
LAMA + LABA + GC	12 (92)	10 (83)
<i>Laboratory parameters</i>		
BNP, mg/l	93 (73.0–185.0)	110 (48.5–152.0)
<i>ECG parameters</i>		
QTc, ms	436.4 ± 19.5	433.2 ± 13.4
QT dispersion, ms	34.9 ± 9.0	37.9 ± 12.1
Values are expressed as mean ± SD, n (%) or median (95% CI). LAMA = Long-acting muscarinic antagonist; LABA = long-acting beta-agonist; GC = glucocorticoids.		

There were no changes in relevant medications potentially influencing cardiac repolarization during the study period.

Surgical Approach, Complications and Hospitalization Time

Of the 12 patients in the intervention group included in the per-protocol analysis, 5 patients received bilateral LVRS of the upper lobes, 2 patients received unilateral LVRS of the right upper lobe and 4 patients received

LVRS of right lower lobe (2 of them received additional resection of one segment of the middle lobe). LVRS on the left lower lobe was performed in 1 subject.

In 2 patients, a pneumothorax occurred after removal of thoracic drainage and resolved without further complications after drainage, and in 2 cases, a persistent fistula had to be oversealed 14 days after LVRS. One of the patients with a persistent fistula had the longest hospitalization time (28 days), while the mean hospitalization time after surgery was 14 days (range 7–28).

Table 2. Primary outcomes

	Control group (n = 13)			Intervention group (n = 12)			Treatment effect (95% CI)	Adjusted treatment effect ^a (95% CI)	p value for adjusted treatment effect
	baseline	follow-up	change	baseline	follow-up	change			
QTc, ms	436.4 ± 19.5	436.4 ± 20.9	-0.0 ± 13.0	433.2 ± 13.4	427.9 ± 13.3	-5.3 ± 10.1	-5.3 (-15.0 to 4.4)	-5.9 (-15.5 to 3.7)	0.214
QT dispersion, ms	34.9 ± 9.0	36.3 ± 11.8	+1.4 ± 13.2	37.9 ± 12.1	33.1 ± 11.5	-4.8 ± 18.9	-6.2 (-19.6 to 7.3)	-3.0 (-13.0 to 7.0)	0.536

^a Adjusted for baseline QTc and QT dispersion, respectively.

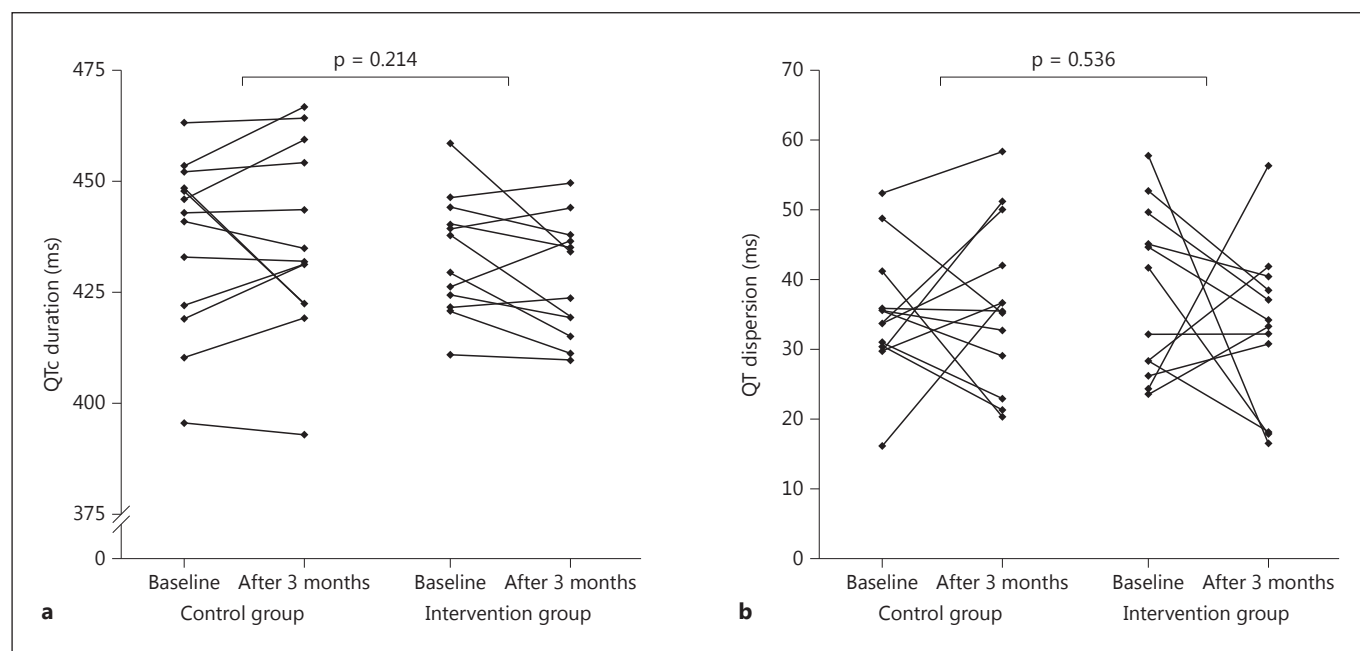


Fig. 3. QTc (**a**) and QT dispersion (**b**) values of individual patients are presented for the control group and the intervention group. The solid bars represent the mean QTc and QT dispersion, respectively, at baseline and after 3 months (control group) and at baseline and after LVRS (intervention group).

Treatment Effect on Cardiac Repolarization Measures

LVRS led to no significant reduction in median QTc of -5.3 ms (95% confidence interval, CI -15.5 to 3.7, $p = 0.214$) and QT dispersion of -3.0 ms (95% CI -13.0 to 7.0, $p = 0.536$), respectively, compared to the control group (table 2). The individual results on QTc duration and QT dispersion according to randomization are illustrated in figure 3a and b, respectively. A post hoc analysis showed no significant interaction between the treatment effect on QTc and QT dispersion, respectively, and age, gender, heart rate, arterial hypertension, arrhythmia, FEV₁ %

pred., SaO₂, the use of antihypertensive medication, the use of beta-blockers and the use of medications affecting the QT interval, respectively.

Only 1 patient in the intervention group and 3 patients in the control group showed a prolonged QTc (>450 ms) at baseline. After LVRS, QTc was normalized in the patient with previously prolonged QTc, whereas in the control group, no relevant changes were observed. No patient showed a prolonged QT dispersion >60 ms at baseline or at follow-up.

Table 3. Possible confounders for treatment effect

	Control group (n = 13)			Intervention group (n = 12)			Adjusted treatment effect ^a (95% CI)	p value
	baseline	follow-up	change ± SD	baseline	follow-up	change ± SD		
<i>Clinical characteristics and cardiovascular risk</i>								
Systolic blood pressure, mm Hg	130.2 ± 11.9	134.2 ± 18.3	+4.0 ± 17.1	129.7 ± 9.3	124.8 ± 19.6	−4.9 ± 16.0	−9.0 (−23.0 to 5.0)	0.198
Diastolic blood pressure, mm Hg	78.7 ± 10.2	81.2 ± 12.3	+2.5 ± 7.3	85.6 ± 9.7	79.9 ± 12.6	−5.7 ± 11.7	−6.9 (−15.4 to 1.6)	0.108
Heart rate, bpm	90.4 ± 15.0	94.1 ± 12.3	+3.6 ± 15.3	78.1 ± 14.8	82.3 ± 12.6	+4.1 ± 13.3	−7.1 (−17.3 to 3.1)	0.164
Pocock risk score, %	2.4 ± 1.4	2.5 ± 1.8	+0.2 ± 0.8	2.1 ± 1.6	2.1 ± 1.5	−0.0 ± 0.6	−0.2 (−0.8 to 0.5)	0.601
<i>Lung function</i>								
FEV ₁ , % pred.	26.2 ± 5.9	24.6 ± 6.5	−1.6 ± 3.9	27.4 ± 5.2	35.7 ± 9.1	+8.3 ± 7.9	+10.0 (4.7 to 15.2)	0.001
FVC, % pred.	68.2 ± 15.7	69.0 ± 16.3	+0.8 ± 11.0	68.1 ± 10.7	84.3 ± 14.8	+16.3 ± 19.1	+15.4 (3.6 to 27.2)	0.013
TLC, % pred.	129.0 (119.0 to 130.0)	121.0 (117.0 to 126.0)	+0.0 (−5.0 to 3.0)	126.0 (118.5 to 150.5)	124.0 (117.0 to 142.5)	−4.0 (−11.0 to 0.5)	+2.8 (−9.3 to 15.0)	0.635
RV/TLC ratio	66.8 ± 5.6	66.6 ± 7.8	−0.2 ± 6.5	68.1 ± 4.6	61.8 ± 5.2	−6.3 ± 7.5	−5.3 (−10.8 to 0.1)	0.053
DLCO, % pred.	34.6 ± 5.1	33.1 ± 5.2	−1.5 ± 4.6	34.0 ± 8.3	37.7 ± 10.3	3.7 ± 8.1	+5.0 (−0.3 to 10.4)	0.064
<i>Blood gas analysis</i>								
SaO ₂ , %	93.7 (91.6 to 95.9)	94.5 (92.2 to 96.0)	+0.1 (−0.5 to 1.4)	94.7 (94.1 to 95.5)	94.8 (92.5 to 96.5)	+0.4 (−0.6 to 2.1)	+0.9 (−0.9 to 2.8)	0.292
<i>Laboratory parameters</i>								
BNP, mg/l	93.0 (73.0 to 185.0)	108.0 (61.0 to 181.0)	+0.0 (−51.0 to 18.0)	109.5 (48.5 to 152.0)	89.5 (59.0 to 131.5)	+5.5 (−32.5 to 47.5)	+31.6 (−46.6 to 109.7)	0.410
^a Adjusted for corresponding baseline value.								

^a Adjusted for corresponding baseline value.

Treatment Effect on Possible Confounders

Table 3 shows the treatment effect on possible confounders. Systolic blood pressure showed a decrease of -9.0 mm Hg (95% CI -23.0 to +5.0, $p = 0.198$) in the intervention group compared to the control group. LVRS led to a relative reduction in mean RV/TLC of $-9 \pm 11\%$ and a relative increase in FEV₁ of $30 \pm 29\%$. No significant differences in the change of SaO₂ were observed.

Association between Treatment Effect on Cardiac Repolarization and Possible Confounders

No significant association between change in QTc and change in possible confounders such as blood pressure, heart rate, Framingham risk score, lung function variables, SaO₂ and BNP was found (online suppl. table S1). The change in QT dispersion was not significantly associated with the change in possible confounders (online suppl. table S2).

Discussion

This is the first RCT evaluating cardiac repolarization in COPD patients. LVRS has been shown to improve breathing mechanics and lung function in patients with severe COPD and emphysema. The findings suggest that LVRS does not influence cardiac repolarization in patients with COPD, and therefore, lung function impairment seems not to be a mechanism for altered cardiac repolarization in COPD patients. However, it still remains unclear if hypoxia may be a mechanism leading to altered cardiac repolarization in patients with COPD.

SCD is a major cause of cardiovascular mortality. Coronary artery disease, cardiomyopathies, congenital heart disease and alteration of cardiac repolarization including the long QT syndrome are established risk factors for SCD [28].

Both, altered QT interval and increased QT dispersion represent predictors of an elevated risk for malignant cardiac arrhythmia and SCD [11, 29]. The QT interval represents the time from onset of ventricular depolarization to completion of repolarization including the vulnerable period for reentry tachycardia. In practice, a QTc prolongation to >450 ms has been identified as a risk factor for fatal ventricular arrhythmias and SCD [29, 30]. QT dispersion is an index of the spatial differences in myocardial recovery times. QT dispersion >60 ms promotes the development of malignant ventricular arrhythmias [17] and SCD [11].

To date, there are no other RCTs investigating possible determinants of altered cardiac repolarization and increased cardiac repolarization dispersion in COPD patients. There are previous cross-sectional studies investigating potential predictors of increased cardiac repolarization dispersion in COPD patients [17, 31–33]. However, the included patients were mostly free from comorbidities. A significant univariate association between QT dispersion and FEV₁ % pred. and FVC % pred., respectively, has been documented in 246 patients with mild-to-moderate COPD [31]. After correcting for covariates, this association did not remain statistically significant. A previous study compared 30 COPD patients with and without increased QT dispersion regarding possible factors influencing QT dispersion and found no factors independently influencing QT dispersion [17]. Consistent with these findings, the previous cross-sectional study by our group showed no significant independent association between QT dispersion and possible influencing factors [5]. Further, in the current study, there was no significant change in QT dispersion after LVRS compared to the control group, and no significant association between QT dispersion and possible determinants changed by LVRS such as lung function and blood pressure was found. Additionally, the current study does not show a significant difference in the change in QTc duration between the intervention and the control group, and no association between possible determinants and QTc duration was found.

The findings of our previous study showed a significant independent association between hypoxia and QTc duration indicating a possible mechanism of altered cardiac repolarization duration in COPD patients [5]. It has been assumed that hypoxia may prolong cardiac repolarization duration. In a study with healthy volunteers by Roche et al. [34] exposing them to normobaric hypoxic conditions, a significantly prolonged QTc interval due to hypoxia was found. Further, prolonged QTc interval was

found in 12 COPD patients with low mean basal SaO₂ (<80%) [35]. In contrast, Sarubbi et al. [33] measured QTc in 15 hypoxemic/hypercapnic COPD patients before and after oxygen therapy and showed no significant reduction of QTc duration after 1 day of oxygen supplementation. Although the results of this RCT cannot confirm hypoxia as a mechanism for altered cardiac repolarization in COPD patients, this might be because there was no significant change in oxygen saturation after LVRS in the current trial. Thus, it is still a matter of debate whether hypoxia affects cardiac repolarization, and the underlying mechanism through which hypoxia may possibly influence cardiac repolarization remains currently unknown.

As a limitation of this study, no continuous 24-hour ECG was performed, and therefore, it is not possible to evaluate cardiac repolarization both during a longer daytime period and during sleep. The study was performed as a sub-analysis of a recently published RCT evaluating the effect of LVRS on endothelial function in severe COPD, and the power analysis was calculated to clarify this specific question [18]. The negative findings of this study may therefore result from a lack of power. However, due to the observed CIs of the treatment effect, a reduction in QTc duration of >15.0 ms and in QT dispersion of >19.6 ms due to LVRS can be excluded. Thus, LVRS seems not to have a clinically significant effect on cardiac repolarization.

Conclusion

This is the first RCT assessing the effect of LVRS on cardiac repolarization in COPD patients. The findings suggest that LVRS does not influence cardiac repolarization in patients with COPD and therefore, lung function impairment seems not to be a mechanism for altered cardiac repolarization in COPD patients. However, it still remains unclear if hypoxia may be a mechanism leading to altered cardiac repolarization in patients with COPD.

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Financial Disclosure and Conflicts of Interest

There are no competing interests.

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